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AtriCure, Inc.
7555 Innovation Way
Mason, OH 45040

CryoAnalgesia Study
CLINICAL STUDY PROTOCOL

Study Number: CP2015-4

Version date: 31May2016/ **Rev:** D

Regulatory Classification: Exempt

Sponsor's Medical Monitor: [redacted]

Lead Principal Investigators: [redacted]

Scientific Advisor: [redacted]

This study will be performed in compliance with the 21 CFR Parts 11 (Electronic Records; Electronic Signatures), 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 803 (Medical Device Reporting), International Conference on Harmonization (ICH) Guideline E6 for Good Clinical Practice (GCP); Declaration of Helsinki; Health Insurance Portability and Accountability Act (HIPAA) regulations; and Applicable state and local laws and regulations.

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INVESTIGATOR SIGNATURE PAGE
I have read, understood, and agree to:

- Ensure that the requirements for obtaining informed consent are met;
- Conduct the clinical study in accordance with this protocol, including applicable local/state laws and regulations;
- Adhere to the publication policy of AtriCure, as stated in the Clinical Study Agreement (CSA), for data collected during this study;
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments;
- Complete all Case Report Forms and study documentation and relevant imaging assessments (as required) promptly to the Sponsor, AtriCure, Inc., or its authorized representatives.

I will ensure that the IRB review complies with governmental requirements and will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without sponsor and IRB approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligation of clinical investigators and all other pertinent requirements of the sponsor and government agencies.

Investigator Signature: I have read and understood the contents of this protocol. I agree to follow and abide by the guidelines set forth in this document.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Please scan, email or fax this signed page to:

[redacted]

PLEASE RETAIN THE ORIGINAL IN YOUR STUDY RECORDS.

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SPONSOR SIGNATURES

Protocol Name:	*cryo*ICE™ CryoAnalgesia Study
Protocol Number:	CP2015-4
Protocol Title:	The *cryo*ICE™ CryoAnalgesia study **F**or pain management in post tho**R**acic procedures via interc**OST**al cryoanalgesia (FROST)
Name of Finished Product(s):	The AtriCure® *cryo*ICE cryo–ablation system [redacted]

Approvals:

[redacted]

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CLINICAL STUDY PROTOCOL SYNOPSIS

Protocol Name:	*cryo*ICE™ CryoAnalgesia Study
Protocol Number:	CP2015-4
Protocol Title:	The *cryo*ICE™ CryoAnalgesia study **F**or pain management in post tho**R**acic procedures via interc**OST**al cryoanalgesia (FROST)
Name of Finished Product(s):	The AtriCure® *cryo*ICE cryo–ablation syste [redacted]
Development Phase:	Exempt, post market
Study Design:	This is a prospective, multicenter, randomized (3:1), blinded study
Indication of Device:	All medical devices used during this study are cleared for commercial distribution and are to be used in accordance with approved product labeling. AtriCure's cryoICE™ cryo-ablation probes are sterile, single use devices intended for use in the cryosurgical treatment of cardiac arrhythmias by freezing target tissues, creating an inflammatory response (cryonecrosis) that blocks the electrical conduction pathway. The probe is also intended for use in blocking pain by temporarily ablating peripheral nerves. The PROBE may be used in conjunction with a standard off-the-shelf nerve stimulator device in applications where precise peripheral nerve location is desired.
Study Objectives:	The objectives of this study are to: 1. To demonstrate that intraoperative intercostal cryoanalgesia provides improved analgesic efficacy in patients undergoing unilateral thoracotomy cardiac procedures as compared to current intraoperative standard of care. 2. Long-term goal is to elucidate complementary strategies for enhanced postoperative pain management of patients at risk for postoperative pulmonary complications from unilateral thoracotomy cardiac procedures. Completion of the proposed study will for the first time demonstrate efficacy of intercostal cryoanalgesia in patients undergoing minimally invasive cardiac procedures. Furthermore, results of this study may have a pivotal role in supporting future clinical outcome trials for intercostal cryoanalgesia therapy.
Number of Subjects (Planned):	Up to 100 subjects will be randomized into this study
Sites:	Up to 5 sites

Patient Population:	Patients undergoing unilateral thoracotomy cardiac procedures
Inclusion Criteria:	Patients satisfying the following criteria will be considered the screening population and will be eligible for participation: 1. Age 18 - 85 years male or female 2. Patients undergoing unilateral thoracotomy cardiac procedures (with the exception of Aortic Aneurysm repair as sole treatment) 3. Acceptable surgical candidate, including use of general anesthesia 4. Willing and able to provide written informed consent 5. Willing and able to return for scheduled follow-up visits
Exclusion Criteria:	Patients satisfying the following criteria will not be eligible for participation: 1. Cardiac valve surgical procedure via conventional full sternotomy 2. Procedures that require a posterolateral thoracotomy 3. Current pregnancy 4. Current use of prescription opioids 5. FEV1 < 40% predicted 6. Documented myocardial infarction within 30 days of signing informed consent 7. Documented psychiatric disease 8. Documented chronic pain syndrome 9. Documented history of substance abuse 10. Patient currently enrolled in another research study that could directly affect results of either study 11. Physical or mental condition that would interfere with patient's self-assessment of pain 12. A medical condition that in the investigator's opinion could adversely impact the patient's participation or safety, conduct of the study, or interferes with the pain assessments
Study Duration:	Anticipated subject duration will be approximately 180 days post index procedure

Study Endpoints:	**Endpoints:** Co-Primary Endpoints: 1. Forced Expiratory Volume (FEV_1) at 48-hours post-surgery 2. Visual Analogue Scale (VAS) pain in the surgical region at 48-hours post-operative Secondary Endpoints: 1. Spirometry assessments including: forced expiratory volume (FEV_1), forced vital capacity (FVC) and slow vital capacity (SVC) at 48-hours post-extubation and other designated time points during hospital admission 2. Pain in the surgical region assessed via a Visual Analogue Scale (VAS) pain at 72-, 96- and 120-hours (as long as patient remains in hospital up to 120-hours) post-operative 3. Allodynia at 3 and 6 months 4. Duration of oral endotracheal intubation defined as hours until patient is extubated from time patient leaves the operating room 5. Patient Controlled Analgesia (PCA) and oral opioid consumption up to each time point (24-, 48, -96 and 120-hours) and total PCA and oral opioid consumption after extubation 6. ICU length of stay and hospital length of stay 7. Ambulatory movement

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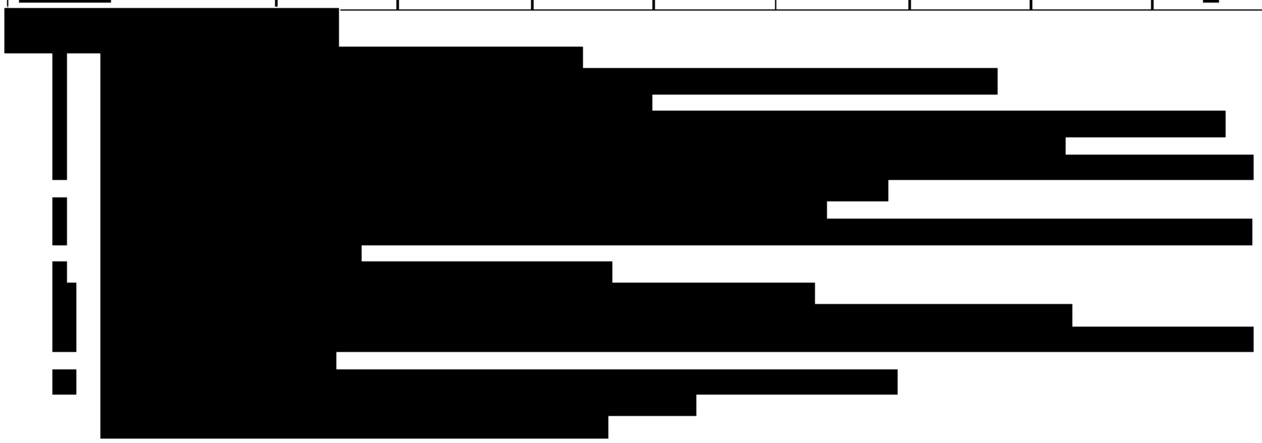
KEY PROTOCOL-SPECIFIC ACRONYMS AND ABBREVIATIONS

Acronyms/Abbreviation	Terms
AE	Adverse Event
CFR	Code of Federal Regulations
CBP	Cardiopulmonary Bypass
CRA	Clinical Research Associate
CTA	Cotton Tip Applicator Test
DLCO	Diffusion Capacity for Carbon Monoxide
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume
FVC	Forced Respiratory Volume
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Information for Use
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IRB	Institutional Review Board
LOS	Length of Stay
MDR	Medical Device Reporting
PI	Principal Investigator
PE	Physical Exam
PHI	Protected Health Information
POPM	Post-operative Pain Management
QS	Quality Systems
SAE	Serious Adverse Event
SAS	Science Analysis System
SOC	Standard of Care
SOP	Standard Operating Procedures
SVC	Slow Vital Capacity
VAS	Visual Analog Scale
VPS	Verbal Pain Scale

[redacted]



ETHICS

Institutional Review Board

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

The study protocol, any protocol amendments, Informed Consent Form (ICF), any ICF amendments, and if applicable, any other written information provided to the subjects e.g., subject recruitment advertising, will be reviewed and approved by an or Institutional Review Board (IRB) prior to implementation of any procedures required solely for the purposes of this study. Each Investigator must obtain IRB approval prior to consent of the first subject.

Prior to site initiation, a signed copy of the IRB approval letter identifying the study and site is required to be submitted to the sponsor signifying study approval.

Each Investigator must also maintain continuous IRB approval. Documentation of approval and renewals must be provided to the Sponsor, and filed on site in the Investigator's Regulatory Binder. Additionally, amendments to the protocol will be submitted for review before implementation except when necessary to eliminate apparent immediate hazards to a subject. IRB approval is required to implement protocol amendments or to resume a suspended clinical investigation.

The occurrence of serious or unanticipated Adverse Events (AEs) during the study must be reported to the IRB.

Applicable Regulations

Regulations are to be followed as applicable including: 21 CFR Parts 11 (Electronic Records; Electronic Signatures), 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 803 (Medical Device Reporting); All surgical products used in this study are commercially available and will be used within current labeling and indications for use. Consequently, this study is not investigational and is exempt from 21CFR Part 54 (Financial Disclosure by Clinical Investigators) and 21CFR Part 812 (Investigational Device Exemptions) with the exception of 21CFR812.119 (Disqualification of a Clinical Investigator); International Conference on Harmonization (ICH) Guideline E6 for Good Clinical Practice (GCP); Declaration of Helsinki; Health Insurance Portability and Accountability Act (HIPAA) regulations; and Applicable state and local laws and regulations.

Subject Information and Consent

This informed consent process applies to participation in the study only (i.e., this process does not include consent required for structural heart surgery). The surgeon will obtain the Institution's standard informed consent for surgery.

In compliance with FDA regulations, no subject shall be enrolled in an investigation without provision of adequate informed consent. The Principal Investigator is responsible for ensuring that each subject enrolled in the study is given adequate informed consent. Failure to obtain and properly document this process is in violation of the US Code of Federal Regulations, the Declaration of Helsinki, and this study protocol.

The ICF must have the approval of the IRB. While some institutions may request for modification of the ICF to satisfy specific institutional requirements, the use of a modified or unique ICF is permitted if it meets the requirement of 21 CFR Part 50 and is approved by the Sponsor. Informed consent of all subjects must be documented on an ICF in the primary language of the subject. All translated consent forms need IRB approval. Eligible U.S. subjects should also sign the Health Insurance Portability & Accountability Act form, if not combined with the ICF.

The Investigator or designee shall carry out the Informed Consent process on those subjects meeting the eligibility criteria. The informed consent process involves the following: giving a subject adequate information concerning the study, providing adequate opportunity (time) for the subject to consider all available options, responding to the subject's questions, ensuring that the subject has comprehended this information and finally, obtaining the subject's consent to participate in this study. All subjects in this study should be completely informed about the purpose, risks, benefits, and other pertinent details of this study. The informed consent process is careful to avoid the perception of any coercion or undue influence on, or inducement of, the subject to participate, and does not waive or appear to waive the subject's legal rights. The ICF is presented in native, non-technical language that is understandable to the subject. The ICF ensures important new information is provided to new and existing subjects throughout the clinical investigation.

The Informed Consent process is finalized by completion of the ICF. Following the explanation of the study intent, the Investigator or designee shall offer to answer any of the subject's questions. If the subject then agrees to participate, his or her willingness must be documented via signatures of the ICF.

This document must be signed and dated by the subject prior to any study related procedures or enrollment. No dates should be pre-populated, or completed by someone other than the person providing the signature. The subject will be provided a copy of the signed informed consent document.

During a subject's participation in the study, the subject will sign and date any amendment(s) to the informed consent document and a copy of the signed document will be provided to them.

STUDY ADMINISTRATIVE STRUCTURE

This study is sponsored by AtriCure, Inc. and will be conducted in the US, under a single protocol approved by an IRB for each site prior to implementation at the study site.

The Principal Investigators (PI) at the study sites are qualified by education, experience and training to assume responsibility for the conduct of this study.

An Electronic Data Capture (EDC) system will be utilized by study site personnel to transfer study data from source records (medical records and/or source document worksheets) onto common electronic case report forms (eCRFs). The EDC system is a web-based, secure electronic software and is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements.

Serious Adverse Events (SAEs) and product quality problems (for products used during the index procedure), including potential and actual product use errors suspected to be associated with the use of a Food and Drug Administration (FDA) regulated drug, biologic, medical device or dietary supplement used during the course of this study will be reported by the PI to applicable authorities including the: 1) Sponsor (AtriCure); 2) IRB; 3) respective manufacturer(s); and/or 4) FDA via MedWatch Online Voluntary Reporting Process or Medical Device Reporting (MDR) as appropriate.

1.0 INTRODUCTION

Intercostal cryoanalgesia is shown to be a safe and effective strategy for post-operative pain management for patients undergoing intrathoracic procedures requiring thoracotomy.[1,2] Right anterior mini-thoracotomy has been advocated as an alternative approach for patients undergoing mitral and aortic valve surgery.[3] Intercostal cryoanalgesia in post-unilateral thoracotomy patients undergoing cardiac procedures has not been evaluated compared to the current standard of postoperative pain management using oral or intravenous opioids.

Post-thoracotomy pain is reported to be one of the most painful surgical incisions currently used,[4,5] due to the combined factors of incisional pain with interruption of muscular, ligamentous, neurovascular bundles, and osseous structures. The application of retractors used during the procedure, continuous pleural irritation and chest wall movements during respiration and coughing with indwelling chest tubes further adds challenges in the balance of optimal analgesia and the risk of side effects.[6] This alters respiratory physiology that may lead to splinting, sputum retention, atelectasis, and chest infections. It represents a major morbidity, because there is currently no single standard technique that can effectively eliminate the pain and associated complications.[7] Adequate post-thoracotomy analgesia can improve respiratory function, improve pulmonary toilet, allow compliance with intensive physiotherapy and prevent some complications.[8]

Several options are available for treatment of post-thoracotomy pain. Conventional analgesia involves intravenous opiates, which is not always completely effective and is associated with several side effects, including mental status changes and respiratory depression.[8] Epidural analgesia is another commonly used form of pain control for post-thoracotomy pain, however full anticoagulation for cardiopulmonary bypass poses a potential risk for epidural hematoma. Also, postoperative patient mobility is reduced while the epidural is in place. Other techniques include intercostal nerve blocks for immediate postoperative pain control. However, intercostal blocks are rarely employed as the sole analgesic technique as they are short lived. In addition, intercostal nerve blocks can result in a high plasma concentration of local anesthetic per volume injection; therefore, care must be taken to avoid toxic levels.

Recent studies have demonstrated the beneficial effect of cryoanalgesia for post-thoracotomy pain in reduction of opioid requirement, reduction in post-operative pain scores, superior hemodynamic recovery (optimization of systolic blood pressure and heart rate, optimization of the pH values of arterial blood gases, and superior pulmonary function (higher FEV_1 and FVC values).[1] Intercostal cryoanalgesia can produce temporary neurolysis for up to two months without long-term histological nerve damage.[2]

We propose to assess whether intra-operative intercostal cryoanalgesia using the *cryo*ICE® probe [redacted] provides superior post-operative analgesic efficacy as compared to current pain management in patients undergoing unilateral thoracotomy cardiac procedures.

2.0 STUDY OBJECTIVES

The objectives of this study are to:

1. To demonstrate that intraoperative intercostal cryoanalgesia provides improved analgesic efficacy in patients undergoing unilateral thoracotomy cardiac procedures as compared to current intraoperative standard of care.
2. Long-term goal is to elucidate complementary strategies for enhanced postoperative pain management of patients at risk for postoperative pulmonary complications from unilateral thoracotomy cardiac procedures.

Completion of the proposed study will for the first time demonstrate efficacy of intra-operative intercostal cryoanalgesia in patients undergoing minimally invasive cardiac procedures. Furthermore, results of this study may have a pivotal role in supporting future clinical outcome trials for intra-operative intercostal cryoanalgesia therapy.

3.0 STUDY ENDPOINTS

The following endpoints will be collected for this study:

Co-Primary Endpoints:

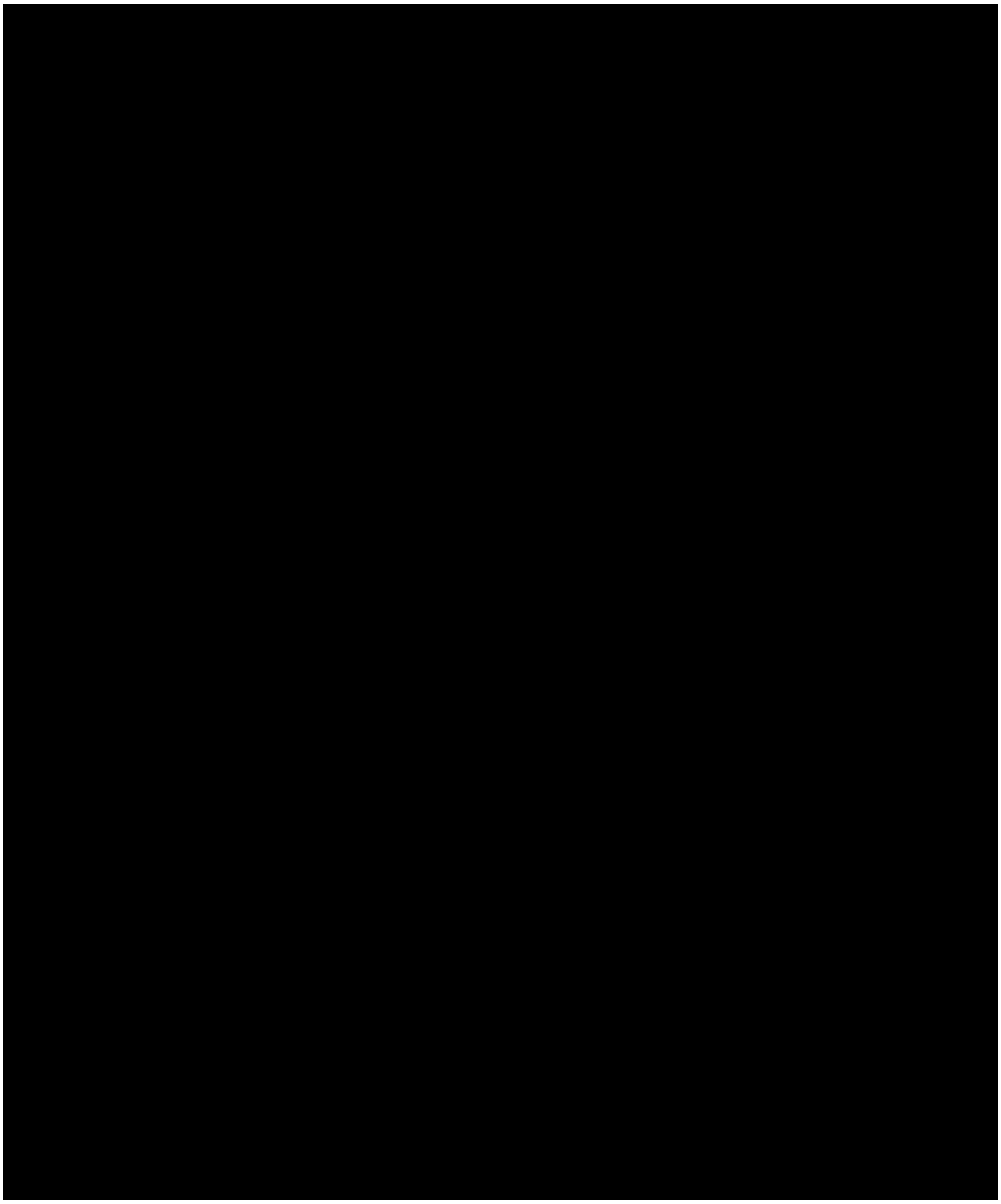
1. Forced Expiratory Volume (FEV_1) at 48-hours post-surgery
2. Visual Analogue Scale (VAS) pain in the surgical region at 48-hours post-operative

Secondary Endpoints:

1. Spirometry assessments including: forced expiratory volume (FEV_1), forced vital capacity (FVC) and slow vital capacity (SVC) at 48-hours post-extubation and other designated time points during hospital admission
2. Pain in the surgical region assessed via a Visual Analogue Scale (VAS) pain at 72-, 96- and 120-hours (as long as patient remains in hospital up to 120-hours) post-operative
3. Allodynia at 3 and 6 months
4. Duration of oral endotracheal intubation defined as hours until patient is extubated from time patient leaves the operating room
5. Patient Controlled Analgesia (PCA) and oral opioid consumption up to each time point (24-, 48, -96 and 120-hours) and total PCA and oral opioid consumption after extubation
6. ICU length of stay and hospital length of stay
7. Ambulatory movement

4.0 INVESTIGATIONAL PLAN

4.1 Overall Study And Design – Subject Disposition Diagram



Overall Study and Design – Description

All patients who are undergoing a unilateral thoracotomy cardiac procedure will be eligible to participate based upon consent and evaluation of the inclusion and exclusion criteria defined in this protocol.

Patient must meet all inclusion/exclusion criteria before randomization and enrollment.

Upon enrollment, subjects will be assigned a sequential identification number at each site and a corresponding sealed envelope which will be opened prior to the procedure to reveal the treatment group. Subjects will be randomized 3:1. Three subjects will receive intercostal cryoanalgesia in conjunction with standard post-operative pain management and one subject will receive standard post-operative pain management only. [redacted]

Two (2) treatment arms result:

- Surgery with intercostal cryoanalgesia + standard POPM – Study Arm
- Surgery without intercostal cryoanalgesia + standard POPM –Control Arm

All subjects, regardless of assigned treatment group, will receive the institutional standard of care for pre-operative, intra-operative and post-operative anesthetic and analgesic standard of care for surgical pain management.

Subjects will be assessed for AEs related to the use of the AtriCure® *cryo*ICE cryo–ablation system and will be instructed to notify the PI of any AEs that occur during the study. Subjects will be followed for approximately 180 days post index procedure.

4.2 Selection of Study Population

4.2.1 Recruitment

All patients who meet the inclusion criteria and sign the ICF will be tracked via EDC in a Screening Log. Patients will be provided the IRB approved ICF and will have the opportunity to read, understand, and have their questions answered prior to signing the ICF. If the patient agrees to participate in the study and signs consent, the ICF will be completed. The subject must sign and date the ICF prior to any study-specific procedures being performed. The person reviewing the ICF with the subject will also sign and date the ICF. The subject will be given a copy of the signed ICF to keep.

Upon entering subject screening information into EDC, each subject will be assigned a unique ID number sequentially in ascending order.

4.2.2 Enrollment

Patients are considered **enrolled** in the study once they have met Inclusion/Exclusion criteria and are randomized.

4.2.3 Inclusion Criteria

Patients satisfying the following criteria will be considered the screening population and will be eligible for participation:

1. Age 18 - 85 years male or female
2. Patients undergoing unilateral thoracotomy cardiac procedures
3. Acceptable surgical candidate, including use of general anesthesia
4. Willing and able to provide written informed consent
5. Willing and able to return for scheduled follow-up visits

4.2.4 Exclusion Criteria

Patients satisfying the following criteria will not be eligible for participation:

1. Cardiac valve surgical procedure via conventional full sternotomy
2. Procedures that require a posterolateral thoracotomy
3. Current pregnancy
4. Current use of prescription opioids
5. FEV1 < 40% predicted
6. Documented myocardial infarction within 30 days of signing informed consent
7. Documented psychiatric disease
8. Documented chronic pain syndrome
9. Documented history of substance abuse
10. Patient currently enrolled in another research study that could directly affect results of either study
11. Physical or mental condition that would interfere with patient's self-assessment of pain
12. A medical condition that in the investigator's opinion could adversely impact the patient's participation or safety, conduct of the study, or interferes with the pain assessments

4.2.5 Removal of Subjects from Study

In accordance with the Declaration of Helsinki and the Code of Federal Regulations, a subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or the institution. Should a subject (or subject's legally authorized guardian/representative) decide to withdraw; all efforts will be made to collect and report the final visit observations as thoroughly and timely as possible. Subjects who withdraw from the study will not be replaced.

The primary reason for early termination and the date of termination will be recorded in the electronic case report form. Reasons may include:

Investigator Decision

If the subject experiences an adverse event and the Principal Investigator or Medical Monitor believes it is in their best interest to discontinue participation in the study, they will be withdrawn from the study.

Lost to Follow-up

When contact with the subject has been lost without completing the final visit assessment, and every attempt to contact has failed, the subject will be considered lost to follow-up. Attempted contact with the subject should include 2 attempted phone calls and the sending of a certified letter before the subject can be considered lost to follow-up. Final documentation regarding all attempts to contact the subject requesting their return for the final visit should be documented.

Withdrawal of Consent

The subject withdraws consent for participation in the study. Any method of contact with the subject in which they state they no longer want to participate in the study specific activities constitutes withdrawal of consent. When possible the reason for withdrawal will be documented.

Site Termination or Study Termination

A site or study may be terminated. When this occurs all subjects at the site will be withdrawn and documented as early termination. Reasons for site or study termination may include, but are not limited to the following:

- Administrative Concerns (e.g., inadequate subject enrollment, Investigator/institution non-compliance, change of business strategy, etc.);
- Safety Issues, including those due to non-compliance, which substantially affect the risk to benefit ratio of the study subjects at a site or for the study as a whole;
- Regulatory Body Mandate(s)

Other (which may include):

- Protocol deviation, noncompliance or violation
- Sponsor recommendation
- Device/index procedure failure
- Death

Subjects that are not extubated or discharged from the hospital by Day 5 Post-Operative will continue to be followed for 180 days post procedure.

5.0 PROCEDURE

5.1 General Description

Individual centers and investigators will be selected based upon their expertise in unilateral thoracotomy cardiac procedures as well as proficiency in cryoanalgesia using the AtriCure® *cryo*ICE cryo–ablation system.

The protocol term "index procedure" refers only to the use of the *cryo*ICE system. All procedures leading up to and after the use of the *cryo*ICE system are considered part of the unilateral cardiac thoracotomy procedure and are to be conducted under the discretion of the surgeon in accordance to the hospital's standard of care.

If the subject meets all study eligibility criteria, they will be enrolled and randomized. If the subject is randomized to the group to receive the Intercostal Analgesia by using the AtriCure® *cryo*ICE cryo–ablation system, the following steps are performed:

Note: A recommended surgical technique is presented below. It is recognized that individual patient anatomic variation, surgical conditions, or surgeon preference may necessitate modifications to the outlined procedures. Regardless, surgeons must adhere to the instructions for use for the AtriCure *cryo*ICE Probe (CRY02) as *outlined in the IFU.*

5.2 Intercostal CryoAnalgesia (Index Procedure)

5.2.1 Control Arm – Surgery without Intercostal Cryoanalgesia + standard POPM

If the subject is randomized to the Control Arm, the subject will receive post-operative pain management as prescribed by the attending physician or institutional standard for post-operative unilateral thoracotomy cardiac surgery patients.

5.2.2 Study Arm – Surgery with Intercostal Cryoanalgesia + standard POPM

If the subject is randomized into the Study Arm, the subject will receive one session of cryoanalgesia

[redacted]

5.2.3 Pain Management for Both Treatment Groups

Pre-operative:

Institutional SOC for pain management will be followed for both study groups in the pre-operative phase.

Intra-operative:

All non-invasive and invasive monitoring, induction of general anesthesia and oral endotracheal intubation will be provided per institutional protocol. All anesthetic techniques, intraoperative TEE examinations, surgical procedures, CPB, and vasoactive infusions in terminating CPB are not impacted by this protocol. The study group and control group will receive treatment as previously outlined.

Post-Operative:

Post -operative pain management will be managed according to the institutional standard of care. The decision to administer additional pain management therapy in the post-operative/follow-up setting is left to the discretion of the Investigator, and his/her assessment of the patient's pain level. All medications taken for all pain management will be captured and recorded in the subject's source documents and on the eCRF.

The use of local post-operative pain management techniques (i.e., intercostal, peri-vertebral, or any other acceptable method) is permitted for both treatment groups up to 24 hours post-operatively according to institutional standard of care.

6.0 IDENTITY OF STUDY DEVICES

The devices utilized for the study include:

The AtriCure® cryoICE cryo–ablation system [redacted]

All medical devices used during this study are cleared for commercial distribution and are to be used in accordance with approved product labeling.

6.1 Product Accountability

Product accountability will not be applicable as the investigator will use commercially available products for this study. Devices will not be provided by the sponsor.

7.0 SUBJECT VISITS

Details for specific subject visit activities are found below and reflect the Schedule of Assessments grid.

7.1 Visit 1 – Baseline

Subjects will be screened for study participation during the baseline visit. The procedures required for the baseline visit may be conducted during more than one visit. The following will be conducted and/or obtained: Some baseline procedures may have been completed as patient standard of care and therefore may be completed prior to informed consent and do not need to be repeated after consent.

The following procedures must be conducted within 30 days prior to the index procedure:

- Informed Consent
- Demographics
- Medical and Surgical History
- Targeted Physical Exam
- Pregnancy Test, as required (within 7 days of procedure)
- Vital Signs
- Height and Weight
- Spirometry
- Concomitant Medication Review
- Inclusion/Exclusion Criteria
- Randomization
- VAS
- Ambulatory Movement

7.2 Visit 2 – Index Procedure

- Targeted Physical Exam (prior to Index Procedure)
- Vital Signs (prior to Index Procedure)
- VAS (prior to Index Procedure)
- Index Procedure (Study Arm - Intercostal Analgesia or Control Arm – SOC Pain Management)
- Concomitant Procedure Type
- Concomitant Medication Review
- Adverse Events Assessment
- Date and Time Subject Exits Surgical Suite

7.3 Visit 3 24 hour Post-Operative Follow-Up Visit

- Vital Signs
- Concomitant Medication Review
- Adverse Event Assessment

7.4 4, 5, 6 and 7 – 48, 72, 96 and 120 Hour Post-Operative Follow-up Visits

- Vital Signs
- Spirometry
- VAS
- Ambulatory Movement
- Concomitant Medication Review
- Adverse Events Assessment

7.5 Visit 8 – Hospital Discharge

- Vital Signs
- Spirometry
- VAS
- Ambulatory Movement
- Concomitant Medication Review
- Adverse Events Assessment
- Date and Time of Discharge from ICU
- Date and Time of Extubation
    - Extubation is anticipated to occur during the first 24 - 36 hours post-op but may occur at any time during hospital stay.
- Date and Time of Hospital Discharge

7.6 Visit 9 – 30 Day Post-Operative Follow-Up Visit

- Vital Signs
- Spirometry
- Concomitant Medication Review
- Adverse Events Assessment

7.7 Visit 10 – 90 Day Post-Operative Follow-Up Visit (Phone call)

- Vital Signs required if subject is seen in the office for allodynia assessment
- Allodynia Screening
- Concomitant Medication Review
- Adverse Events Assessment

7.8 Visit 11 – 180 Day Post-Operative Follow-Up Visit (Phone call)

- Vital Signs required if subject is seen in the office for allodynia assessment

- Allodynia Screening
- Concomitant Medication Review
- Adverse Events Assessment
- Study Exit (See 7.9)

7.9 Study Exit

At study exit the following must be collected.

- Study Exit Date
- Exit Reason

7.10 Allodynia Visits

Allodynia screening questions will be included at the 90 and 180 day visits. If the questions elicit a positive response, the subjects will be asked to make an office visit for a more thorough allodynia assessment. Vital signs will be collected along with the allodynia assessment.

7.11 Repeated Study Visit Tests

All study procedures should be conducted at the investigational site.

Targeted Physical Examination: A targeted physical exam (PE) includes an assessment of the following body systems: General Appearance, Cardiovascular, Respiratory, and Musculoskeletal. A more thorough PE may be conducted according to institutional SOC. If any findings are noted during the PE, the finding should be recorded in the source documents as medical history or as an adverse event, as appropriate. The finding shall be recorded in the eCRF as required per the Safety section of the protocol.

Vital Signs: Vital signs should be taken in accordance with institutional SOC and include pulse rate, blood pressure, temperature and respiration rate.

Height/Weight: Height and weight should be taken in accordance with institutional SOC. BMI will be calculated automatically by the EDC based on the height and weight taken at Visit 1.

Spirometry: Spirometry assessments including: forced expiratory volume (FEV_1) forced vital capacity (FVC) and slow vital capacity (SVC). To allow for consistency across study sites, these spirometry measurements will captured on a commercially available bedside device provided by AtriCure.

Ambulatory movement: Ambulatory movement assessed by "Yes- Independently", "No" or "Yes - with assistance" responses to the following questions:

- Is patient able to sit up in bed?
- Is patient able to stand up?
- Is patient able to walk?

Ambulatory movement will also be assessed via "shoulder flexion movement" of "Limited ROM", "Full ROM" or "Unable". Ambulatory movement will be collected individually for each shoulder.

Visual Analog Scale (VAS): The Visual Analogue Scale and Mankoski Pain Scale Definitions are found in Appendix 1. The subject should be asked to complete the scale to rate their current pain level for general pain intensity. In addition, the subject should be asked to complete the scale to rate their current pain level for pain intensity related to the surgical region. The person conducting the test at the site should be blinded as to treatment group.

Concomitant Medication Review: All medications, including vitamins or nutritional supplements currently prescribed to, or taken by, the subject shall be recorded in the subject's source documents. Only medications taken for pain management therapy need to be reported on the eCRFs.

Adverse Event Assessment: All adverse events shall be recorded in the subject's source documents. Only adverse events that are related to the intercostal analgesia procedure or the AtriCure® cryoICE cryo–ablation system need to be reported on the eCRFs. Refer to description of collection of Adverse Events for additional information.

Allodynia Screening: As part of the 90 and 180 day follow-up visit, a series of questions will be asked of the subject to determine if an in-office visit is necessary to further evaluate the presence of allodynia.

Allodynia Assessment: Cotton Tip Applicator (CTA) Test. See Appendix 2 for instructions. The same person at the site should administer the test at each time point and should be blinded as to treatment group.

8.0 DATA MANAGEMENT AND INTEGRITY

8.1 Data Completion and Record Keeping

8.1.1 Source Documents

Source documents are documents on which information regarding subjects are first recorded. PI subject files or hospital records generally are the basis of source document information. This may include but is not limited to, original subject files, hospital/clinic records, original recordings/tracing, digital images from automated instruments, X-ray films, and laboratory results.

Source documents must be retained by the PI as part of the subject's permanent medical record. The information in the source documents is used to complete the eCRFs. All information captured on the eCRFs should be completely and accurately supported in source documentation. Study Monitors will verify data reported on eCRFs with site source documents. Any additional information relevant to the study should be included in the source documents. In particular, any deviations from the study protocol or procedures should be recorded in the source documents. The PI will retain originals of all source documents, subject consent forms, and study data.

8.1.2 Data Collection

An EDC system will be utilized by study site personnel to transfer study data from source records (medical records and/or source document worksheets) onto common eCRFs. This system is a web-based,

secure electronic software application This system is designed, developed, and maintained in a manner that is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements. The platform software has been validated in accordance with 21 CFR Part 11, European Commission's Directive on Data Protection and US Safe Harbor Certification. Prior to being released for data entry, validation of the study level components (i.e. data entry screens, associated edit checks and work flow) will be conducted in accordance with approved user acceptance testing procedures. Access to this system will be controlled so that only authorized users will have the ability to enter into the system. The system is considered a closed system according to 21 CFR Part 11 Electronic Records; Electronic Signatures.

The EDC system will be used to facilitate the collection of all study data at the site. Designated site personnel will be responsible for entering subject data into the EDC system. All external and Sponsor internal users will be trained on the EDC application at a level dependent on their planned function.

An EDC digital User Manual will be available under the help menu within the EDC website to assist in the collection and entry of source data into the electronic casebook.

Investigative study sites will be asked to enter subject data into the eCRFs no later than 2 weeks from the time the subject was seen for their scheduled study visit.

Detailed description of the eCRF components are included in the eCRF Completion Instructions. These will be provided to the Investigators prior to initiating subject enrollment. The respective eCRFs must be fully completed for each subject and signed electronically.

Data collected during the clinical investigation for each subject will be maintained as accurately and completely as possible with entries into an electronic data capture system provided by AtriCure. The personal data recorded on all documents, including copy documents, and within the system will be regarded as confidential. The Investigator will be responsible for the timing, completeness and accuracy of the details entered within the electronic data capture system. All data entered in the database must have source documents in the subject's medical records.

Data will be entered into the electronic data capture system by members of the Investigational team who have received training in the use of the system. The system will generate data queries at the point of data entry based on validation checks defined by AtriCure. Such validation checks will primarily be focused on validation of key variables including selected subject demographics, appropriate value ranges and date checks. Resolution of the queries will be the responsibility of the Clinical Investigator and investigation team members. Following completion of all data queries on each eCRF, the Clinical Investigator will be responsible for reviewing and confirming agreement to the data within the system.

The Investigator must record the subject's participation in this clinical investigation in the subject's hospital notes. In addition, the Investigator must keep a separate list of all subjects entered into this clinical investigation showing each subject's name, date of birth and assigned subject number (for identification purposes). A subject Identification Log will be provided in the Investigator's File for this purpose.

8.1.3 Data Correction

Corrections to eCRFs will be prompted via automated electronic edit checks and queries manually created by reviewers. The corrections and the individual making the correction(s) to the eCRF will be within EDC.

8.1.4 Investigator Regulatory Binder

Each Investigator must maintain an accurate, complete, and current copy of the Investigator Regulatory Binder. Upon receipt of copies of changes or revision updates to the Binder from the Sponsor, the Investigator will add the updated document to the Regulatory Binder. If an Investigator holds multiple copies of the Regulatory Binder, then all copies must be updated with the current revisions.

8.1.5 Study Correspondence

Each Investigator and all personnel from the investigational site will maintain records of all correspondence, electronic, written, and verbal, relating to any aspect of the clinical investigation. The records are maintained in the Investigator regulatory Binder consisting of, but not limited to correspondence with other participating clinical investigators, the reviewing IRB, and the Sponsor. The CRA will examine the contents of the correspondence.

8.1.6 Data Privacy

Subjects will be made aware that their personal data will be collected and processed in accordance with data protection legislation including the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Subjects will be asked to sign an Authorization for Release of Personal Health Information (PHI) for the purpose of this investigation. This authorization may be combined with the ICF depending on local IRB preference. Results from the Clinical Investigation may be published. However, subject confidentiality will be maintained at all times and it will not be possible to identify individual subjects from any data presented.

8.1.7 Record Retention, Inspection, and Custody

The PI must maintain all documentation related to the study until notified by the Sponsor. The PI will allow representatives of the Sponsor, IRB, the FDA, or other government regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals during the study. These inspections are to verify adherence to the protocol, integrity of the data being captured on the eCRFs, and compliance with applicable regulations.

Subject medical records will be kept confidential. Study reports will not identify subjects by name. These reports may be submitted to the FDA and/or regulatory authorities.

If custody of the records is transferred, notice of such a transfer should be given to the Sponsor no later than ten (10) working days after the transfer occurs.

The Investigator should retain copies of all documents pertaining to this clinical investigation (including source documentation, the informed consent document and any other documents to identify the subjects) for at least 2 years after this clinical investigation is completed. In addition, if the Clinical Investigator moves/retires, etc., he/she should provide AtriCure Inc. the name and address of the person who will look after and be responsible for the subjects' clinical investigation related records.

8.1.8 Medical Dictionary Coding

Medical dictionary coding will be performed using a coding thesaurus algorithm. The MedDRA will be

used upon data entry and query resolution for AEs, SAEs, via automated and manual coding processes.

8.1.9 Data Quality Assurance

Quality control and quality assurance processes implemented during this study to ensure subject safety rights, and welfare are protected and to foster data integrity are characterized below.

8.1.10 Investigator Training - Protocol Specific Training

Protocol training will be scheduled once IRB approval is obtained and the Clinical Study Agreement is executed. AtriCure, Inc. will train the study site on the protocol and that training will be documented. It is ultimately the responsibility of the Investigator to ensure all clinical site personnel participating in this study are trained.

The index procedure may only be performed by qualified investigators, familiar with the study procedures and techniques.

Investigators will also be required to complete training in the use of the AtriCure® *cryo*ICE cryo–ablation system through didactic and hands on training, including review of an instructional video on the use of the AtriCure® *cryo*ICE cryo–ablation system.

8.1.11 Monitoring

This study will be monitored by the sponsor to ensure:

- The rights, safety and well-being of the subjects are protected;
- The reported study data is accurate, complete, and verifiable from source documents; and
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), applicable GCPs, and with applicable local/regional regulatory requirements.

AtriCure, as Sponsor of this study, will be responsible for monitoring this study. The Clinical Research Associate (CRA) duties are to aid the Principal Investigator in the production and maintenance of complete, legible, well-organized and easily retrievable data. In addition, the CRA will be responsible for assuring the Principal Investigator understands the protocol and all applicable regulations. Approaches to monitoring include on-site visits and may include a remote visit, as appropriate and the rationale and frequency for monitoring will be at the Sponsor's discretion. The extent and nature of monitoring will be predetermined and based on considerations such as the objective, design, complexity, and endpoints of the study and mutually agreed to by the Sponsor. The frequency of monitoring will be determined for each site based on factors including: the planned enrollment, the rate of enrollment, and the current study conduct. Study conduct can be evaluated remotely based on compliance percentage, discrepancy rate and discrepancy type. CRAs will be trained on and comply with established standard operating procedures as well as a written monitoring plan specified by the Sponsor.

In order to perform the monitoring role effectively, the CRA must verify eCRF entries with source documents. The CRA must be given access to primary subject data which supports the information recorded on the eCRF, i.e. hospital notes, appointment books, original laboratory records, etc. Access to these documents must also be given should the regulatory authority in the instance of an external inspection. Since a subject has the right to refuse access to these documents on the grounds of

confidentiality, consent to access is included in the informed consent document, which the subject signs.

The Principal Investigator will receive reasonable notification prior to each monitoring visit during the course of this clinical investigation. At each visit, the Principal Investigator will be expected to co-operate with the CRA for the review and verification of eCRFs and any additional records that may have been previously arranged between the Principal Investigator and the CRA.

8.2 Changes to Protocol, Protocol Deviations and Protocol Amendments

8.2.1 Changes to Protocol

The Investigator should not implement any deviation from, or changes to the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in CRA(s), change of telephone number(s)). In the event of an emergency situation, the Investigator must notify the CRA or AtriCure immediately. A full written report of the situation must be forwarded to the IRB who approved the original protocol and AtriCure within 10 working days of the event.

8.2.2 Protocol Deviations

The Investigator agrees to conduct the study in accordance with this protocol; however, protocol deviations may occur during the course of the study. Protocol deviations are events occurring during the conduct of the study which are not in compliance with the protocol and for which an amendment has not been granted. Protocol deviations can be committed by the Sponsor, the PI, or study subject. A deviation can be identified from a number of sources. Potential sources include, but are not limited to: a member of the PI's staff, the CRA during monitoring visits, or a member of the data management or statistical groups when entering or analyzing data. The PI or PI's representative are encouraged to contact the CRA or AtriCure as soon as possible upon observing a protocol deviation. Regardless of the source, it is crucial to document the deviation and record all corrective actions. Protocol deviations will be reported in the final report.

The process for capturing deviations will be detailed in the monitoring plan. The process will require that documentation describe the deviation, appropriate actions taken, and will be included in the study file for the respective PI and subject. The study site representative will be advised to record the deviation and relevant discussion with the Sponsor about the deviation in subject source documents.

Protocol deviations affecting the scientific soundness of the study or the rights, safety, or welfare of the subjects, will be reported by the PI, as required by the IRB.

Protocol deviations will be summarized and grouped into relevant categories for analysis and may include, but not be limited to, subjects who:

- Entered the study although they did not satisfy the eligibility criteria; or
- Developed withdrawal criteria during the study, but not removed.

8.2.3 Protocol Amendments

If it becomes necessary to amend the protocol then the nature of the amendment will be agreed between the Sponsor and the Principal Investigator(s) and this will be recorded with a justification for the

amendment. The appropriate IRBs will be informed of amendments prior to implementation of the change.

9.0 STATISTICAL METHODS

9.1 Clinical Study Objective

The objectives of this study are to:

1. To demonstrate that intraoperative intercostal cryoanalgesia provides improved analgesic efficacy in patients undergoing unilateral thoracotomy cardiac procedures as compared to current intraoperative standard of care.
2. Long-term goal is to elucidate complementary strategies for enhanced postoperative pain management of patients at risk for postoperative pulmonary complications from unilateral thoracotomy cardiac procedures.

Completion of the proposed study will for the first time demonstrate efficacy of intercostal cryoanalgesia in patients undergoing minimally invasive heart valve surgery. Furthermore, results of this study may have a pivotal role in supporting future clinical outcome trials for intercostal cryoanalgesia therapy.

9.2 Study Endpoints

The following endpoints will be collected for this study:

Co-Primary Endpoints:

1. Forced Expiratory Volume (FEV_1) at 48-hours post-surgery
2. Visual Analogue Scale (VAS) pain in the surgical region at 48-hours post-operative

Secondary Endpoints:

1. Spirometry assessments including: forced expiratory volume (FEV_1), forced vital capacity (FVC) and slow vital capacity (SVC) at 48-hours post-extubation and other designated time points during hospital admission
2. Pain in the surgical region assessed via Visual Analogue Scale (VAS) pain at 72-, 96- and 120-hours (as long as patient remains in hospital up to 120-hours) post-operative
3. Allodynia at 3 and 6 months
4. Duration of oral endotracheal intubation defined as hours until patient is extubated from time patient leaves the operating room
5. Patient Controlled Analgesia (PCA) and oral opioid consumption up to each time point (24-, 48, -96 and 120-hours) and total PCA and oral opioid consumption after extubation
6. ICU length of stay and hospital length of stay
7. Ambulatory movement

9.3 Sample Size and Power

In a couple of previous studies[10,11] of cyro-analgesia on patients undergoing thoracotomy the authors FEV1 was collected at 48-hours post-procedure and at other specified time-points. The studies reported 48-hours FEV1 mean (SD) values of 1.5 (0.7) and 1.1 (0.47) in their standard of care (continuous analgesia and

epidural fentanyl infusions) groups. We used a mean mid-point of 1.3 and a liberal standard deviation of 0.39 as reasonable estimates for sample size calculation. The investigators participating in this trial agree that based on their prior experience a 20% improved FEV1 value (compared to SOC) is a reasonable expectation. Based on this assumption, the expected mean (SD) for the Study Group is 1.56 (0.39), assuming a common standard deviation.

This is a prospective, multicenter, randomized (3:1). Group sample sizes of 75 (Study Group) and 25 (Control Group) will achieve 80% power to reject the null hypothesis of equal means when the population mean difference is 0.26 with a standard deviation for both groups of 0.39 and with a significance level (alpha) of 0.05 using a two-sided two-sample equal-variance t-test.

Also, in a previous preliminary observational study of six patients undergoing single cardiac valve surgical procedure via right anterior mini-thoracotomy comparing a Visual Analogue Scale (VAS of 0-10) pain was collected at 0, 24, and 48 hours post-procedure. Mean VAS pain differences of 1.5 and 1.8 between the intercostal Cryoanalgesia group and the SOC group at 24 and 48 hours were statistically significant with p-values of 0.03 and 0.04, respectively. The common standard deviation at 48 hours post-procedure was 2.2.

Group sample sizes of 75 (Study Group) and 25 (Control Group) will achieve 94% power to reject the null hypothesis of equal means when the population mean difference is 1.8 with a standard deviation for both groups of 2.2 and with a significance level (alpha) of 0.050 using a two-sided two-sample equal-variance t-test.

9.4 Randomization

Upon enrollment, subjects will be assigned a sequential identification number at each site and a corresponding sealed envelope which will be opened prior to the procedure to reveal the treatment group. Subjects will be randomized 3:1 (3 intercostal Cryoanalgesia in conjunction with SOC and 1 SOC). Randomization sequences will be generated by AtriCure Statistician using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and will be stratified by site.

9.5 Analysis Populations

Intent-To-Treat (ITT) Population: The effectiveness, safety and health economics analyses will be based on the ITT population. The ITT Population is defined as all subjects randomized to either the Study Group or SOC Group and on whom the surgical index procedure is attempted (even if the index procedure is aborted).

Per-Protocol (PP) Population: A PP population may be defined for effectiveness and health economics and analyses. This population is defined by ITT population but without any major protocol violations, that is, those that could potentially bias the results.

9.6 Analysis of Study Endpoints

Study endpoints will be summarized by treatment group and overall as appropriate. Continuous variables will be summarized by presenting the number of subjects, mean, standard deviation, median, minimum, maximum by procedure group (Study Group or SOC Group). Tabulation of categorical variables by group will include counts and percentages. 95% confidence intervals will be provided as appropriate.

Since this is an exploratory study, additional analyses, additional analysis populations, covariates and

summary tables and/or graphs will be generated as needed.

In all analyses described below, the null hypothesis will be a two-sided test of no treatment group difference. All statistical tests will use a two-sided significance level of α=0.05.

9.6.1 Effectiveness and Health Economic Analysis

A two-sided student's t-test will be used to compare the FEV1 means between the two procedure groups at 48-hours post-surgery. 95% CI will also be reported. A Shapiro-Wilk test of normality will be performed and if the normality assumption is not met, an approximate non-parametric model (e.g. Wilcoxon rank-sum test) may be performed. Similarly, a two-sided student's t-test will be used to compare the VAS pain means between the two procedure groups at 48 hours post-surgery. 95% CI will also be reported. A Shapiro-Wilk test of normality will be performed and if the normality assumption is not met, an approximate non-parametric model (e.g. Wilcoxon rank-sum test) may be performed.

Hourly VAS pain at day of surgery, 72-, 96- and 120-hours post-surgery will be similarly analyzed. In addition, a repeated measures ANOVA model including sites (or clusters of sites), procedure (Study Group and SOC Group), time, and procedure group-by-time interaction will be used to analyze the mean pain over time. The compound symmetry, autoregressive order one, and unstructured will be used to model the covariance structure. The covariance structure producing the lowest Akaike's Information Criterion (AIC) and Schwarz' Bayesian Criterion (SBC) values will be selected. Effects with p-values < 0.05 will be removed from the model and the data will be reanalyzed.

Other variables: duration of oral endotracheal intubation, PCA opioids, FVC, SVC, ICU length of stay (LOS) and overall hospital LOS, will be analyzed via ANOVA models taking as independent variables baseline characteristics, sites (or clusters of sites), sex, age, and other variables as seem appropriate.

A Pearson's Chi-Squared test will be used to compare the incidence of allodynia events between the two procedure groups at 3- and 6-months post-surgery. Alternatively, a Fisher's Exact test will be used if justified by small cell counts (less than 5) and Clopper-Pearson (Exact) 95% CI will also be reported. Ambulatory movement will be similarly summarized and analyzed.

Assumptions of hypothesis tests such as for normality and homogeneity of variance will be performed. In the event that the assumptions are severely violated, the nonparametric equivalent test may be reported along with the appropriate justification.

9.6.2 Safety Analysis

AEs related to the CryoAnalgesia procedure or device will be reported on the eCRF. These AEs will be listed and descriptively summarized for patients in the Study Group. No formal statistical hypothesis will be tested.

9.7 Detailed Analysis Plan

Prior to looking at the data and database closure, if needed, a detailed statistical analysis plan will be prepared and finalized to completely specify the statistical procedures to be applied to the data by the statistician who will conduct the analysis. The plan will amplify on the methods discussed in this protocol, will address any protocol changes that would affect the analysis, and will provide a rationale for any changes to the analysis.

10.0 Safety Monitoring

Subject safety will be monitored throughout the course of this study by monitoring for Adverse Events and Product Complaints related to the AtriCure *cryo*ICE Probe (CRY02) used in conjunction with the *cryo*ICE BOX (v6). The AtriCure *cryo*ICE Probe (CRY02) used during the index procedure for the clinical study has been cleared for marketing by the FDA and is being used within the current labeling and indications for use. Any event that occurs that may have caused or contributed to a death or serious injury or that indicates the AtriCure *cryo*ICE Probe (CRY02) device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur will be reported in compliance with 21 CRF Part 803.

In addition to general surgical risks, additional risks specifically associated with the AtriCure *cryo*ICE Probe (CRY02) are as follows:

- Skin injury due to cryoablation of skin
- Intercostal muscle injury
- Permanent peripheral nerve damage

These risks could lead to symptoms that include:

- Numbness around the incision lasting from 1 to 6 months
- Neuralgia occurring 6 weeks after cryoanalgesia, lasting up to 2 months
- Hyperesthesia

There may also be other risks that are unforeseen at this time. The complete Risk/Benefit Assessment is found in Appendix 3.

10.1 Adverse Events

10.1.1 Definition of an Adverse Event

Adverse Event (AE): any undesirable clinical occurrence or change from a patient's baseline (pre-index procedure) condition, whether it is device related or not.

Adverse Event Identification: a condition that is one of the following:

a. A unique symptom or event that is a change from the subject's baseline status
b. A series of symptoms or events that can be categorized as a single entity based on definitions found herein
c. A specific diagnosis responsible for a clinical change
d. A worsening or exacerbation of a pre-existing condition

10.2 Serious Adverse Events

10.2.1 Definition of a Serious Adverse Event

Serious Adverse Event (SAE): any adverse event is considered serious if it results in death, is life threatening, requires hospitalization (initial or prolonged), results in disability or permanent damage, causes congenital anomaly/birth defect, requires intervention to prevent impairment or damage, or other serious (important medical events) which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

Note: "Death" should not be reported as an adverse event. The cause of death should be reported as an

adverse event. The only exception is "Sudden Death" when the cause is unknown.

10.2.2 Subject Death

Subject death during the investigation must be reported by the Investigator (or designee) by submitting the Adverse Event eCRF to the Sponsor, within 24 hours of learning of the adverse event. The electronic Adverse Event Form must be electronically signed by the Investigator. A copy of the death records, death certificates and an autopsy report (if performed) are required to be sent to the AtriCure or designee within 10 days following the death. Any death must be reported to the FDA within 10 working days of AtriCure or designee's knowledge of the death. In addition, subject death must be reported to the IRB in accordance with IRB requirements.

10.2.3 Adverse Event Classification

The investigator is required to provide:

- Time interval of the event – The time interval of the occurrence of the adverse event should be assessed in relationship to timing of the index procedure (Use of the AtriCure® cryoICE cryo–ablation system)
- Date of event onset and outcome of the event, or date of death
- Severity of the event – (Mild, Moderate, Severe)
- Action taken for medical management of the event

Relationship of the event – it is the PIs responsibility to assess the relationship of an AE and provide primary cause. Events will be categorized by relationship to the AtriCure *cryo*ICE Probe (CRY02) device, the *cryo*ICE BOX (v6), an ancillary device, the index procedure or other.

- Adverse events will be assessed to determine if the event meets the definition of a serious adverse event.

10.2.4 Reporting Adverse and Serious Adverse Events

The investigator (or designee) will record all AEs (both serious and non-serious and regardless of relationship) in the source documents. The Investigator at each site participating site is responsible for reporting AEs and SAEs to AtriCure only when they are related to the CryoAnalgesia index procedure or device. AEs related to the CryoAnalgesia procedure or device will be reported on the eCRF. The CRFs allow the investigator to indicate whether or not the adverse events are related to the device or index procedure.

- Use a separate Adverse Event Form to document each event
- The Adverse Event Form must be electronically signed by the Investigator
  Note: It is the responsibility of the Investigator to inform their IRB of SAEs as required by their IRB procedures and in conformance with FDA requirements.

All Serious Adverse Events that are related to the CryoAnalgesia index procedure or device must be reported by the Investigator by submitting the AE eCRF to AtriCure within 10 days of becoming aware of the AE. An event determined by the Investigator to be life threatening or to have led to death should be reported within 24 hours.

The Investigator shall send a written report including a narrative description of the SAE to AtriCure within three (3) working days of the initial report. The Investigator should follow all unresolved SAEs

until the events are resolved, or the subject has exited the study or the AE is otherwise explained.

11.0 PRODUCT COMPLAINTS

11.1 Medical Device Reporting and Product Complaints

All reported device observations, malfunctions or failures for CryoAnalgesia products will be reported [redacted]

Whenever an event involving an AtriCure device is subject to reporting under that Medical Device Reporting (MDR) regulation, AtriCure shall submit to the FDA the appropriate reports required by MDR within the time frames as identified in 21 CFR Part 803. Criteria for reporting malfunctions and potentially serious injuries is based on interpretations of medical intervention, potential for serious injury, and impact of a malfunction to a device's essential functionality. AtriCure will follow - reference documents (QS-007, MDR/Reportable Incident Reporting and QS-006, Complaint Procedure) medical device in compliance with reporting, 21 CFR Part 803 and 21 CFR Part 820: Code of Federal Regulations, Quality System Regulations.

11.2 Source Of Product Complaint Data

Means of obtaining product complaint data include review of the subject's medical records or observation by the PI and/or study staff or the CRA.

12.0 STUDY OVERSIGHT

12.1 Independent Oversight

No independent oversight is anticipated for this study.

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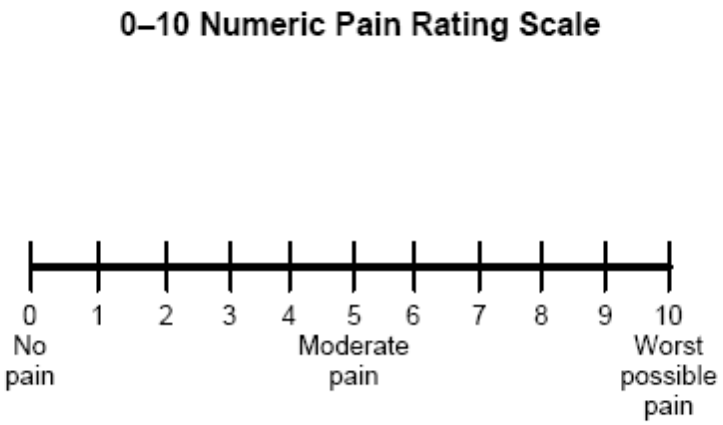
13.0 Appendices

APPENDIX 1 - Visual Analog Scale



Mankoski Pain Scale Definitions

0- Pain Free
1- Very minor annoyance- occasional minor twinges. No medication needed.
2- Minor annoyance- occasional strong twinges. No medication needed.
3- Annoying enough to be distracting. Mild painkillers take care of it. (Aspirin, Ibuprofen.)
4- Can be ignored if you are really involved in your work, but still distracting. Mild painkillers remove pain for 3-4 hours.
5- Can't be ignored for more than 30 minutes. Mild painkillers ameliorate pain for 3-4 hours.
6- Can't be ignored for any length of time, but you can still go to work and participate in social activities. Stronger painkillers (Codeine, narcotics) reduce pain for 3-4 hours.
7- Makes it difficult to concentrate, interferes with sleep. You can still function with effort. Stronger painkillers are only partially effective.
8- Physical activity severely limited. You can read and converse with effort. Nausea and dizziness set in as factors of pain.
9- Unable to speak. Crying out or moaning uncontrollably- near delirium.
10- Unconscious. Pain makes you pass out.

APPENDIX 2 – ALLODYNIA ASSESSMENT

Allodynia and *hyperpathia* are terms used to describe the hypersensitivity that occurs with neuropathic pain. Many different techniques have been used to assess skins sensitivity, including alcohol pads, Von Frey fibers, and camel hair brushes (https://www.youtube.com/watch?v=-eRSx0Cbxks). Recently, the use of a cotton tip applicator (CTA) has been described to test skin sensitivity to evaluate abdominal wall allodynia due to chronic pelvic pain (1). This simple test has been validated as a reproducable screening method to identify cutaneous allodynia in women with or without chronic pelvic pain (2), and we propose to use this same simple test to evaluate neuropathic pain following chest wall surgery. For a video of the technique used to evaluate chronic pelvic pain, please see http://www.jove.com/video/1232/demonstration-cutaneous-allodynia-association-with-chronic-pelvic.

1. An explanation of the test is undertaken and permission to proceed is obtained.

2. The patient exposes the chest wall at the surgical site.

3. A disposable sterile cotton-tipped applicator is shown to the patient and brushed against the patient's hand to demonstrate how the light pressure will feel.

4. The cotton-tipped culture stick is then lightly drawn down the chest wall in the anterior axillary line, the mid axillary line, and the posterior axillary line, as well as the anterior and posterior extents of the incision. The patient is asked to note the point at which light pressure applied to the skin becomes sharp as the cotton-tipped culture stick is drawn down the chest wall, starting approximately 2 rib interspaces above the surgical incision, and continuing at least 3 interspaces below the surgical site.

5. The patient will either note the presence of normal sensation or will note a sudden and discrete sharpness in sensation. A positive test is defined by the presence of this sudden sharp sensation. A small mark with a marking pen will be used to map the border of the area of sensitivity. The process should be repeated until the entire area of cutaneous allodynia has been identified. The furthest "north, south, east and west" points will be marked around the incision. A photograph of the area of sensitivity may be taken to document increasing or decreasing areas of allodynia, but is not required.

6. The north south east and west points will be measured for height and width in centimeters (cm).

7. In some cases the areas are large but in others they will be small. Some areas may encompass the entire length of the incision, while others may involve only a very small, specific site.

1. Jarrell J. Demonstration of cutaneous allodynia in association with chronic pelvic pain. J Vis Exp. 2009(28).
2. Nasr-Esfahani M, Jarrell J. Cotton-tipped applicator test: validity and reliability in chronic pelvic pain. Am J Obstet Gynecol. 2013;208(1):52.e1-5.

APPENDIX 3 - RISK/BENEFIT ASSESSMENT

Clinical Risk/ Benefit Assessment

SUMMARY

The cryoICE™ CryoAnalgesia study is being undertaken to examine pain management in post thoracic procedures via intercostal cryoanalgesia. Subjects meeting the inclusion/exclusion criteria and undergoing unilateral thoracotomy cardiac procedures will participate in this study. The risks of participation are offset by the significant potential for clinical and functional benefits.

POTENTIAL BENEFITS

The potential benefit to study subjects outweighs the risks of participation in this study.
The benefits may include but are not limited to, the following:

- Clinical improvement - patients may experience improved post-operative pain control following minimally invasive heart valve surgery
- Functional improvement - patients may experience less post-operative pulmonary complications, less mental status changes, improved blood pressure and heart rate
- Overall advancement of medical and scientific knowledge - Information obtained from this study may further our understanding of peri-operative pain control following this surgical procedure and improve patient post-operative experience.

There may also be other benefits that are unforeseen at this time.

POTENTIAL RISKS

Risk Category: **Minimal**

Independent from this research study, the participant is already scheduled to undergo a minimally invasive heart valve surgical procedure via right mini-thoracotomy. All risks for this procedure will have been discussed with the surgeon and surgical consent will have been signed. Similarly, common anesthetic risks will have been discussed, and anesthetic consent will have been signed. The participant will be fully informed of the risks of this study. Possible adverse events may include, but are not limited to, the following.

Risks of Intercostal Cryoanalgesia with the cryoICE® probe:

Most frequent (occurring more than 10% of the time):

- Device Breakage
- Skin injury due to cryoablation minor damage of skin that would heal over time
- Intercostal muscle injury
- Permanent peripheral nerve damage resulting in difference in sensation not evident prior to surgery
- Failure to ablate peripheral nerve may result patient requiring pain management

Less frequent (occurring 1-10% of the time):

- Tissue perforation
- Tissue freezing

Rare (occurring less than 1% of the time):

- Injury to user
- Nitrous gas exposure to patient

There may also be other risks that are unforeseen at this time.

MINIMIZATION OF RISKS

Measures which will be taken to minimize risks related to the study include:

- Investigators will be chosen that are qualified to complete study index procedures and are experienced in use of cryoICE cryo-ablation system.
- Well defined clinical study protocol, including specific inclusion/ exclusion criteria to enroll appropriate subjects in the trial.
- Close patient monitoring during the surgical procedure and follow-up period.

Alternative to Participation:

Patients may decline and would be treated with the same standard of care.

CONCLUSION

This clinical study is justified because the study sponsor and clinical investigators believe the potential benefits outweigh the potential risks.